Please cancel claim 6, without prejudice and without disclaimer.

REMARKS

Claims 1-15, 23, 25-44 and 49-53 were examined in the Office Action dated August 20, 1998 (Paper No. 14) and rejected under (1) 35 U.S.C. §112, first paragraph as nonenabled (claims 13-15 and 43-44); (2) 35 U.S.C. §112, second paragraph as indefinite (claims 1-8, 10-15, 23, 25-44 and 49-51); (3) 35 U.S.C. §102(a) as anticipated (claims 1-2, 4-6, 8-12 and 13-15); and (4) 35 U.S.C. §103 as obvious (claims 3, 7, 23, 25-44 and 52-53). These rejections are believed to be overcome by the foregoing amendments and are otherwise traversed for the reasons discussed below.

Overview of the Above Amendments and New Claims:

The claims have been amended to recite the subject invention with greater particularity. Claims 1, 13, 25 and 27 have been amended to incorporate definitions present in the application in order to clarify the meaning of the phrase "a polypeptide having the biological activity of" the reference molecule.

Claim 23 has been amended to replace the term "package" with "container." The remaining amendments are made in order to conform the language of certain dependent claims to the language of amended claims 1 and 25.

Support for the foregoing amendments may be found in the claims as filed, as well as throughout the specification at, *inter alia*, page 8, line 26 through page 10, line 2.

No new matter has been added to the application by way of the foregoing amendments.

Claim 6 has been canceled. Cancellation is made without intent to acquiesce in the Office's rejections and in order to hasten prosecution. Applicant reserves the right to bring the claims again in a subsequent, related application.

Formal Matters:

The Office requested applicant resolve an inconsistency regarding the claim for priority in the application and the Declaration filed. Applicant is in the process of obtaining a Substitute Declaration which includes a reference to provisional applications 60/005,075 and 60/021,540 and will forward this document to the Office as soon as it is obtained.

Rejections Under 35 U.S.C. §112, First Paragraph:

Claims 13-15 and 43-44 were rejected under 35 U.S.C. §112, first paragraph, the Office alleging that no guidance or example of a method of preventing epithelial cell damage using PDGF, KGF, IGF and/or IGFBP is given. In particular, the Office asserts that it is unpredictable whether these factors "would have a preventative effect for epithelial cell damage, at which dose, under which conditions of application, for how long and for which type of cell damage." Office Action, page 3. However, applicant submits that the claims are fully enabled.

In this regard, applicant notes its charge under 35 U.S.C. §112, first paragraph is to provide a specification which teaches one of ordinary skill in the art *how to make and use* the claimed invention without "undue experimentation." *In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993). Applicant submits that a sufficient disclosure has indeed been provided regarding *how to make* the compositions

for use in the claimed methods. The Office is directed to pages 16-17, bridging paragraph; and page 18, line 19 through page 31, line 22, for teachings regarding obtaining the subject growth factors. Applicant has also provided sufficient disclosure regarding *how to use* the compositions. The Office's attention is drawn to pages 15-16, bridging paragraph, page 16, lines 11-17; page 17, line 26 through page 18, line 18; and page 31, line 24 through page 40, line 27, for an extensive discussion regarding how to formulate and administer the compositions of the present invention, including appropriate doses to be administered. Applicant submits that one of skill in the art could readily determine appropriate concentrations and doses to use for particular preventative applications.

Thus, the specification indeed teaches *how to make and use* the invention in terms which correspond in scope to the claims. This disclosure must be taken as complying with the first paragraph of §112 unless the Office can establish that there is reason to doubt the objective truth of the statements relied upon therein for enabling support. *In re Marzocchi*, 169 USPQ 367 (CCPA 1971).

The Office also states it seems "unpredictable if not impossible to prevent burn wounds by the claimed methods." Office Action, page 3. However, the claims which are subject to the rejection are not limited to methods of preventing burns. One can readily envision a whole host of indications other than burns where preventing epithelial cell damage would be desirable. For example, the methods could be used, *inter alia*, to prevent ulcers which often occur chronically, as well as in conjunction with therapies known to cause epithelial cell damage, such as surgery or certain laser treatments.

In making the present rejection, then, it appears the Patent Office is attempting to impose a requirement upon applicant not only to show how to make and use the claimed compositions, but also to establish an unerring *degree of effectiveness* of such formulations. This requirement far exceeds applicant's statutory obligations under §112. These are the kinds of questions that the Food and Drug Administration--the agency Congress has created to administrate safety and efficacy standards in pharmaceutical formulations intended for human applications--is intended to address. These are not the kinds of questions which the Patent Office should be asking in assessing enablement under 35 U.S.C. §112. See, e.g., *In re Brana*, 34 USPQ 1436 (Fed. Cir. 1995) and the Examiner Guidelines for Biotech Applications, 60 Fed. Reg. 97 (1995). Accordingly, applicant submits that this rejection is improper and should be withdrawn.

Rejections Under 35 U.S.C. §112, Second Paragraph:

Claims 1-8, 10-15, 23, 25-44 and 49-51 were rejected under 35 U.S.C. §112, second paragraph as indefinite. With respect to claims 1-12, 25-44 and 49-53, the Office argues: "Even though the applicants define the biological activities of the growth factors, starting page 8, line 26, and exemplify what these molecules can be, there are other growth factors or molecules having the same biological activities of stimulating the growth of cells in the dermis..." Office Action, page 3. Claims 3, 7, 25, 27, 30 and 32 were also rejected based on the terminology a polypeptide "having the biological activity of" the reference molecule. However, applicant respectfully submits that the present claims are indeed clear and definite.

In this regard, claims 1, 13, 25 and 27 have been amended to incorporate definitions present in the application in order to clarify the meaning of the phrase "a polypeptide having the biological activity of" the reference molecule. All of the remaining claims subject to this rejection ultimately depend from the amended claims. Accordingly, this basis for rejection is believed to be overcome.

Claims 25 and 27 were also rejected under 35 U.S.C. §112, second paragraph as indefinite based on the recitation "polynucleotide" therein. These claims have been amended to substitute the term "polypeptide" for "polynucleotide." Thus, this basis for rejection has also been overcome.

Finally, claim 23 was considered indefinite based on the terminology "package." Although applicant submits that one of skill in the art would readily understand the meaning of the term "package" in this context, claim 23 has been amended to recite "container." Therefore, this basis for rejection is also believed to be overcome.

Withdrawal of the rejections under 35 U.S.C. §112, second paragraph is respectfully requested.

Rejection Under 35 U.S.C. §102(a):

Claims 1-2, 4-6, 8-12 and 13-15 were rejected under 35 U.S.C. §102(a) as anticipated by Ring et al., abstract from the Fifth Annual Meeting of the Wound Healing Society, Minneapolis, MN, April 27-30, 1995 ("Ring"). The Office argues: "Ring et al. teach a combination of rPDGF and rKGF that results in a significant increase in new epithelial area in the treatment of burns." Office Action, page 4. However, applicant submits that the present claims are not anticipated by Ring.

In particular, claims 1 and 13 have now been amended to incorporate recitations from the specification, including the subject matter of claim 7, in a Markush group. Specifically, the claims now recite that the KGF polypeptide is selected from the group consisting of "a biologically active fragment of a full-length KGF, a biologically active analog of a KGF comprising at least one amino acid substitution, deletion or addition, and a biologically active derivative of a KGF." Ring does not relate to the use of any such KGF molecules, but appears to use full-length recombinant KGF. In fact, claim 7, which recites that the KGF molecule is a "biologically active fragment of a full-length KGF polypeptide," was not subject to this rejection, indicating that the Office recognizes Ring does not pertain to the use of KGF fragments. Thus, this basis for rejection is believed to be overcome and withdrawal thereof is respectfully requested.

Rejections Under 35 U.S.C. §103:

Claims 3, 7, 23, 25-44 and 52-53 were rejected under 35 U.S.C. §103(a), as unpatentable over Ring, in view of Martin et al., *Prog. Growth Factor Res.* (1992) 4:25-44 ("Martin"), U.S. Patent No. 4,861,757 to Antoniades et al. ("Antoniades"), U.S. Patent No. 5,677,278 to Gospodarowicz et al. ("Gospodarowicz"), Jyung et al., *Surgery* (1994) 115:233-239 ("Jyung") and U.S. Patent No. 5,624,893 to Yanni ("Yanni").

The Office asserts that Ring teaches "a combination of rPDGF and rKGF that results in a significant increase in new epithelial area in the treatment of burns";
Martin teaches "PDGF might only act in synergy with other growth factors to enhance wound healing" and "KGF acts in normal epithelial proliferation"; Antoniades teaches "a

method for healing an external would comprising applying a composition that comprises PDGF and IGF-I"; Gospodarowicz teaches a truncated KGF with "at least twice the mitogenic activity of full length KGF"; Jyung teaches "the combination of IGF-I with IGFBP-I has a potent effect on wound healing in rats"; and Yanni teaches a method of treating corneal haze due to scar formation or altered wound healing using PDGF-BB, PDGF-AA, PDGF-AB, KGF, IGF-I and IGF-II. Office Action, pages 5-6. However, applicant respectfully submits that the Office has failed to establish a *prima facie* case of obviousness and that this basis for rejection should be withdrawn.

In particular, the Court of Appeals for the Federal Circuit has stated:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that [the invention] should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art [citations omitted]. Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure.

In re Dow Chemical, 5 USPQ2d 1529, 1531-1532 (Fed. Cir. 1988) (emphasis added). Applicant respectfully submits that, according to this criterion, a *prima facie* case of obviousness has not been established because an expectation of success has not been found in the prior art, but rather in the subject application.

In this regard, although the primary reference speaks to the use of PDGF and KGF, there is absolutely no suggestion in this or any of the other references to use PDGF in combination with a biologically active fragment of a full-length KGF, a biologically active analog of a KGF comprising at least one amino acid substitution, deletion or

addition, or a biologically active derivative of a KGF, as presently claimed. None of the cited art suggests or discloses that such a combination would be desirable.

Particularly, as explained above, Ring does not relate to the use of any such KGF molecules, but rather appears to use full-length recombinant KGF. Martin, at page 31, end of first paragraph, merely speculates that KGF "may act as a paracrine mediator of normal epithelial proliferation." Although Martin states at page 33 that PDGF might act in synergy with other growth factors in some systems, nowhere does Martin suggest the use of PDGF in combination with KGF or any of the other recited components in the present claims. The statement in Martin regarding PDGF is made in a completely different context than that regarding KGF. Antoniades and Jyung do not even pertain to KGF. Yanni relates to the use of topical ophthalmic compositions for treating corneal haze and pain following laser irradiation. As previously explained to the Office, the exemplified compositions in Yanni contain bradykinin antagonists or neurokinin-1 antagonists. Although the passages cited by the Office specify that wound healing modulators may be used in the compositions, these passages only name the modulators in a laundry list of compounds and do not disclose the specific combinations encompassed by the present claims. Hence, dozens of conceivable combinations could be formulated from the list of components given at, e.g., column 7, lines 45-48 of Yanni. However, Yanni does not provide any guidance with respect to which of the possible combinations, from the laundry list of possible substituents, would be most desirable. Finally, Gospodarowicz, while relating to a truncated KGF molecule, does not pertain to compositions containing PDGF and KGF, and, optionally, IGFs and/or IGFBPs.

None of the cited art, either alone or in combination, discloses or suggests applicant's unique combination. It is well known that mixtures of therapeutic agents can fail to be as effective as individual components due to physical interactions of the individual agents which might result in altered conformation, aggregation or precipitation. Competition between component substances is also known to occur. Indeed, the FDA requires that the efficacy of mixtures be shown even if the efficacy of the individual components has been demonstrated, further evidencing the unpredictable results obtained with mixtures versus individual agents. As is readily seen, the efficacy of mixed compositions cannot be predicted.

Thus, although the references individually may disclose pieces of the combination, none of these references gives either a suggestion or an expectation of success for the use of a combined formulation as claimed. Applicant reiterates that the rejection appears to be based on hindsight reconstruction of the invention, using applicant's disclosure as a template. The very fact that the Office relies on six references in making this rejection is evidence, in and of itself, that the Office is piecing together the teachings of the prior art to arrive at applicant's claimed invention. This it cannot do. See, e.g., *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992) and *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

Based on the foregoing, applicant submits that the stated combination is improper and that this basis for rejection should be withdrawn.

Claims 49-51 were rejected under 35 U.S.C. §103(a) as unpatentable over Ring in view of Martin, Antoniades, Gospodarowicz, Jyung, Yanni, and further in view of U.S. Patent No. 5,399,361 to Song et al. ("Song"). Ring, Martin,

Antoniades, Gospodarowicz, Jyung and Yanni are applied as above. Song is said to teach sponges "for enhancing wound healing, that comprise various growth factors, including PDGF, KGF, IGF-1 and IGF-2." Office Action, page 7. However, as with the combination above, applicant submits that the Office has failed to set forth a *prima facie* case of obviousness.

As discussed above, the combination of Ring in view of Martin, Antoniades, Gospodarowicz, Jyung and Yanni is not believed to render the present claims obvious. Song relates to collagen sponges containing an active ingredient. The only exemplified substance used with the sponge is PDGF. As with Yanni discussed above, Song merely mentions PDGF, KGF, IGF-1 and IGF-2 in a laundry list of substances found at column 2, lines 47-49 of the application. There is absolutely no suggestion to combine more than one of the listed substances into the sponge.

Applicant reiterates that without both a suggestion and an expectation of success founded solely in the prior art, this rejection cannot stand. Thus, withdrawal thereof is respectfully requested.

Conclusion

Applicant respectfully submits that the claims are novel and nonobvious over the art and define an invention which complies with the requirements of 35 U.S.C. §112. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated.

Please direct all further communications in this application to:

Joseph H. Guth
Chiron Corporation
Intellectual Property - R440
P.O. Box 8097
Emeryville, CA 94662-8097
Telephone: (510) 923-3888
Facsimile: (510) 655-3542

Respectfully submitted,

Date: 2/22/99 By: _____
Roberta L. Robins
Registration No. 33,208

ROBINS & ASSOCIATES
90 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 325-7812
Fax: (650) 325-7823